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Review

Surgeon and haematologist: A review of comprehensive care for patients with inherited bleeding disorders in Northern Ireland

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ABSTRACT

Background: Management of patients with inherited bleeding disorders has improved since the introduction of Comprehensive Care Centres (CCC) in the United Kingdom (UK). In the event such patients need surgery, the aim of the multidisciplinary team is to facilitate outcomes as good as what would be expected in a non-bleeding disorder patient. A review of such comprehensive care was carried out in patients with inherited bleeding disorders when they needed surgery at Northern Ireland CCC. Aims of the study were to evaluate surgical morbidity and mortality in these patients.
Methods: All patients with inherited bleeding disorders who underwent non-orthopaedic surgery between 2008 and 2012 were identified from the CCC records within the Belfast Health and Social Care Trust (BHSCT) in Northern Ireland (NI) and their case records reviewed.
Results: 28 patients received elective and emergency surgery during this period. There was minimum morbidity and no mortality in this cohort.
Conclusions: Surgery in patients with inherited bleeding disorders has become safe with the advent of multidisciplinary CCCs. Close communication between surgeon and haematologist is key in the successful management of these complex patients.

1. Introduction

Surgery in patients with inherited bleeding disorders is traditionally considered high risk.[1,2] However, the establishment of Comprehensive Care Centres (CCC) in the UK for the management of inherited bleeding disorders has led to considerably improved outcomes.[3]

Inherited bleeding disorders are rare and complex, mainly comprising of haemophilia and Von Willebrand Disease (VWD). Haemophilia is a life-long condition that is potentially debilitating, but a child with haemophilia born today can envisage a normal life expectancy and a good quality of life due to the availability of effective treatment in the form replacement therapy with recombinant or plasma-derived clotting factors.[4] There are two main forms of haemophilia: haemophilia A (average incidence 1:5000 males) and haemophilia B (average incidence 1:25000 males). Whilst the advent of effective and safe prophylaxis has reduced long term joint disease for those with the more severe form, delaying the need for orthopaedic surgery,[5] it has not altered the need for general surgical interventions. VWD, despite being more common, is generally considered a milder bleeding disorder affecting both males and females with average incidence of 1:1000. Although, severe VWD (type 3) can be a more significant bleeding disorder than mild Haemophilia A. Other clinically important inherited bleeding disorders include deficiencies of coagulation factors V, X, and XI and platelet disorders.[6]

Inherited bleeding disorders require wide-ranging care and effective management within a multidisciplinary team setting. The modern treatments of inherited bleeding disorders are now remarkably effective and, although expensive, their provision with high standards has been made possible by the development of Comprehensive Care Centres (CCC) across the UK.[7] The Haemophilia Alliance is a United Kingdom wide partnership between patients with inherited bleeding disorders and healthcare professionals involved in the delivery of haemophilia care. The Alliance produced "National Service

Abbreviations: CCC, comprehensive care centre; UK, United Kingdom; NI, Northern Ireland; BHSCT, Belfast health and social care trust; NSAIDs, non-steroidal anti-inflammatory drugs; DVT, deep vein thrombosis; VTE, venous thromboembolism; vCJD, variant Creutzfeldt–Jakob disease; HIV, human immunodeficiency virus; VWD, Von Willebrand disease; HC, haemophilia centre.

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Specification for Haemophilia and Other Inherited Bleeding Disorders" in 2001 which was updated in 2006.[8] The aim of these guidelines was to provide a consistently high quality and comprehensive care for haemophilia patients across the UK. The service specifications have recommended that a CCC must have the provision of a general and specialist surgeon in order to manage these patients with very special needs. Surgery in patients with inherited bleeding disorders is complex and these procedures should be performed at a regional centre with expertise and provision of a multidisciplinary team.

There are 280 adult patients registered with inherited bleeding disorders in the relatively stable population of NI (Table 1), not including known carriers, in contrast to only 43 reported in 1959.[9] This five-fold increase in registered cases is most likely a result of improved detection and registration rather than actual increase in incidence. A brief comparison of historical and current management of haemophilia and related disorders is given in Table 2.[10,11]

Comprehensive care for these patients takes place via the BHSCT. Whilst the CCC is based at the Belfast City Hospital, surgery is spread across the three acute hospital sites; Belfast City Hospital, Royal Victoria Hospital, Mater Hospital and elective orthopaedic surgery at Musgrave Park Hospital. Patients are referred to specific consultant surgical teams to ensure an expertise can be developed rather than many consultant teams seeing very few patients. General surgical procedures can be performed with low morbidity and mortality when there is appropriate factor replacement and good support from the haematology team.[12]

We present our experience of NI CCC, with specific emphasis on the management of these patients when they need general surgery (orthopaedic and endoscopic procedures excluded). A close collaboration and team work between the surgeon and haematologist is the key towards an optimum outcome for these patients. The aim of this review was to evaluate morbidity and mortality associated with general surgical procedures in adult inherited bleeding disorders patients managed within NI CCC.

2. Materials and methods

Patients with an inherited bleeding disorder who underwent non-orthopaedic general surgery between 2008 and 2012 were identified from the CCC records within the Belfast Health and Social Care Trust (BHSCT). Patients undergoing routine endoscopy procedures were excluded. Patients with haemophilia, VWD and platelet disorders were included. The case notes of these patients were examined.

3. Results

Twenty eight patients (a total of 29 procedures) were identified who had undergone surgery during the specified period in the NI CCC (Table 3). Twelve patients underwent general surgical procedures, 9 had vascular surgery and 7 patients underwent ENT/maxillofacial procedures. The cohort of patients comprised 17 patients with haemophilia, 9 with VWD and two with a primary platelet disorder. All patients undergoing elective surgery were seen by a consultant haematologist prior to referral to the surgeons. The surgical episode was led by the haematology team. The surgical team was informed of the patient's condition and the risk of bleeding and infection status (vCJD, Hepatitis C, HIV) and a written management protocol was produced for individual patients.

A specific bleeding diathesis management protocol was devised for individual patients (see components of the protocol in discussion). Local or regional anaesthesia, intramuscular injections, aspirin, warfarin, non-steroidal anti-inflammatory drugs (NSAIDs) and low molecular weight heparin for deep vein thrombosis (DVT) prophylaxis were avoided. Instead, patients were advised on mechanical thromboprophylaxis and given early mobilisation for VTE prophylaxis.

Four of 28 patients developed post-operative complications including two wound infections and two bleeding complications. The bleeding complications included a patient who developed wound haematoma which required evacuation ten days after the surgery. The second patient continued to bleed after ligasure haemorrhoidectomy and returned to theatre ten days after the surgery for haemostasis. In both cases, a bleeding point was identified and secured. Excessive peri-operative bleeding was not seen in either of the patients. Neither of the patients required blood transfusion or additional clotting factors on top of what had already been calculated to meet their particular needs. There were no delayed discharges. There was no mortality in this series.

Table 1
Haemophilia and related bleeding disorders in Northern Ireland.

Bleeding disorder	Known affected adults (>16 years) patients in N Ireland (*n* 280)
Haemophilia A	157
Haemophilia B	13
Von Willebrand Disease	92
Platelet disorders	7
Other factor deficiencies	11

4. Discussion

Following guidance in a UK National Health Service (NHS) circular in the early 1990s,[13] inherited bleeding disorders care in the UK has been organised into 24 CCCs and 51 smaller Haemophilia Centres (HCs). A CCC is defined as a centre with at least 40 patients with severe haemophilia that can offer the full range of specialised health services required for the effective management of these patients. The number of 40 was agreed at the time of writing the NHS guideline by a group of senior haemophilia consultants as this was deemed to be the minimum number of patients required for a centre to develop and maintain expertise in the management of haemophilia.[14] In providing general and specialist surgery, it is recommended that these procedures should be performed at a centre with expertise and which provides a comprehensive care programme. The UK treatment strategy for VWD is based on consensus guidelines produced by the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) relating to the diagnosis and management of VWD.[15]

Our experience from NI highlights the importance of an effectively working CCC. Effective communication and team work between surgeon and haematologist has led to minimal morbidity and no mortality in the surgical management of patients with inherited bleeding disorders. This is a similar finding reported by multiple studies in different specialities of surgery such as orthopaedic surgery,[5,16] cardiothoracic,[17] urology[18] and recently liver transplantation.[19]

Patients are reviewed two weeks prior to major surgery and their weight, base line blood tests including relevant clotting factor levels, inhibitor screen and viral screen are checked. Medication is reviewed and, should the patient be taking NSAIDs or any herbal medication, these are stopped as both have an anti-platelet effect which could potentially worsen the haemorrhagic complications of the surgery.

Elective surgery is discussed between the haematology and surgical teams and a surgical protocol is drawn up by the haematology team. This is designed to ensure that all members of the multidisciplinary team looking after the patient are fully acquainted and aware of their requirements. The surgical protocol has several key elements:

Table 2
Haemophilia: Now and Then.

Modern nomenclature	Historical nomenclature	Hereditary nature	Deficiency	Clinical severity	Management in 1960	Management in 2011
Haemophilia A	Classic haemophilia – antihaemophilic globulin deficiency	X-linked recessive males	Factor VIII	Mild to severe	Fresh frozen plasma or fresh whole blood	Recombinant factor VIII DDAVP[a]
Haemophilia B	Christmas disease	X-linked recessive males	Factor IX	Mild to moderate	Fresh frozen plasma or fresh whole blood	Recombinant factor IX
Haemophilia C	Ashkenazic Jewish haemophilia	Autosomal recessive	Factor XI	Mild to moderate	Fresh frozen plasma or fresh whole blood	Plasma derived factor XI concentrate
Von Willebrand disease	Previously believed to have been caused by a functional abnormality of the capillaries. (pseudohaemophilia)	Most commonly autosomal dominant male and female	Von Willebrand factor	Variable depending on subtype	No specific treatment	Factor VIII/Von Willebrand factor complex or DDAVP

[a] Desmopressin (Deamino-D-arginine vasopressin).

- *Patient Demographics*. As the surgery may take place at a different site to the CCC, it is important to include standard information including the patient's full name, date of birth, address and diagnosis. The Health and Care Number is used rather than the patient's hospital number. We also include the blood group and any relevant known antibodies which may complicate the cross match.
- *Category Three Status*. Whilst the population of patients with inherited bleeding disorders who have been infected historically with hepatitis and HIV is not expanding,[20] this

Table 3
Summary of patients managed at Belfast CCC.

	Patient	Diagnosis	Procedure	Complications	Management of complication
1	41 years male	Severe haemophilia A	Repair of popliteal artery pseudo-aneurysm	Wound cellulitis 4 weeks post op	Conservative with antibiotics
2	72 years male	Mild haemophilia B	Right carotid endarterectomy	Continued ooze from neck wound	Evacuation of haematoma post op day 10
3	16 years female	Obligate affected carrier of haemophilia A	Laparoscopic appendicectomy	Pelvic collection	Conservative management
4	61 years male	VWD type 2A	Ligasure haemorrhoidectomy	Continued rectal bleeding till post op day 10	Examination under anaesthesia and haemostasis
5	29 years female	VWD type 1	Laparoscopic cholecystectomy	None	
6	29 years female	VWD type 1	Excision supratentorial neurocytoma	None	
7	61 years male	VWD type 2A	Defunctioning ileostomy	None	
8	61 years male	VWD type 2A	Reversal of ileostomy	None	
9	43 years male	Mild haemophilia A	Laparoscopic cholecystectomy for cholecystitis	None	
10	45 years female	Symptomatic carrier of haemophilia B	Laparoscopic cholecystectomy for biliary colic	None	
11	63 years male	VWD type 2A	Right inguinal hernia repair	None	
12	33 years male	Haemophilia A	Right inguinal hernia repair	None	
13	42 years male	VWD type 2A	Paraumblical hernia repair	None	
14	57 years female	Haemophilia A affected carrier	Excision of sebaceous cyst	None	
15	42 years female	VWD type 2N	Varicose veins surgery	None	
16	39 years male	Severe haemophilia A with inhibitor	Insertion of Portacath	None	
17	37 years female[a]	Obligate affected carrier haemophilia A	Partial thyroidectomy and neck dissection	None	
18	50 years male	Severe haemophilia A	Insertion of Portacath	None	
19	50 years male	Severe haemophilia A	Removal of portacath/insertion Hickman line	None	
20	48 years male	Mild haemophilia A FVIII	Right leg varicose veins surgery	None	
21	42 years female	Hermansky Pudlak syndrome	Excision of submandibular gland	None	
22	34 years female[a]	Obligate affected carrier haemophilia A	Partial thyroidectomy and neck dissection	None	
23	52 years male	Mild haemophilia A	Laparoscopic cholecystectomy and exploration of CBD	None	
24	49 years male	Severe haemophilia A	Insertion Hickman line	None	
25	62 years male	Mild haemophilia A	Left carotid endarterectomy	None	
26	72 years female	VWD type 2A	Laparoscopic cholecystectomy	None	
27	35 years male	Mild haemophilia A	Excision cholesteatoma	None	
28	26 years male	Bernard Soullier syndrome	Excision right supraclavicular lymph node	None	

[a] Both patients required further surgery due to persistently positive disease following high dose iodine.

information is essential for all healthcare professionals. More recently, the main area of focus has been patient's vCJD status.[21] It is important that the theatre and infection control teams are aware of patients deemed to be a public health risk for vCJD and protective precautions and disposable instruments are used where appropriate.

- *Type of surgery*. The haematology team should be made fully aware of the exact nature of the surgery, its duration and expected blood loss in a patient with a similar pathology but without the bleeding disorder, so that appropriate amount of factor replacement can be calculated. Surgical instrument management for those deemed to be a public health risk for vCJD should be discussed to avoid unnecessary quarantining.
- *Pre-operative management*. The detail of necessary clotting factor replacement is provided including its type, dose, timing and who will infuse the factors in the pre and post-operative period. The type of factor VIII administered is important as this dictates the type of laboratory test (one stage or two stage clotting assay) used to check plasma levels post-infusion. In addition, certain Factor VIII gene mutations that cause haemophilia A result in discrepancies between assays requiring that patients should be genotyped. To achieve haemostasis for major surgical procedures in haemophilia, the aim is to achieve an initial plasma factor VIII level of 60–100 IU/dL. For VWD, a plasma VWF activity of around 100 IU/dL is required in the perioperative period with the level maintained at greater than 50 IU/dL in the postoperative period. For patients with mild haemophilia A and type 1 VWD, a documented response to DDAVP should be obtained ahead of the planned surgery. This level is checked and confirmed prior to the surgery. Infusion of clotting factor and checks on plasma clotting factor level are provided by a specialist haematology nurse who remains available for the entire surgical episode.

In general, clotting factor VIII and factor IX concentrates are given as an initial bolus followed by a continuous infusion. Infusion of factor VIII concentrate at a dose of 2–4 U/kg/h can maintain stable plasma levels but it is important to re-check the level throughout the surgery and in the immediate postoperative period as the rate of consumption may be increased if additional blood loss occurs. Continuous infusion offers the advantage of consistent levels, less frequent monitoring, and decreased factor utilization. A similar effect has been noted with factor IX concentrates. Antifibrinolytic therapy may be indicated alongside factor replacement to further reduce the risk of haemorrhage. Other treatment options, depending on the surgery and the patient's underlying bleeding disorder, include desmopressin, Von Willebrand factor concentrate, or activated recombinant factor VII. Regional anaesthesia is relatively contraindicated even with factor concentrate administration. Regional anaesthesia may be offered to some patients with extensive comorbid conditions. However, this would only be undertaken with onsite access to a haematology laboratory as factor levels need to be checked throughout the surgery. This would not be required if the patient receives general anaesthesia.

Clotting factor levels should not exceed the limits stated above due to an increased risk of venous thrombosis.

- *Peri-operative management*. This section contains all the emergency telephone numbers for contact if excessive bleeding is encountered. The haematology registrar and consultant are available out of hours for emergency consults. It also highlights whether further concentrates are required to be given during the surgery. This tends to occur if the surgery is expected to exceed 4 h.
- *Post-operative management*. If required, factor levels are advised to be checked at the time of completion of the surgery. Blood is taken from a peripheral vein and every effort is made to ensure the sample is free from heparin contamination. A clotting factor level of 100% is the aim. The rate of consumption of clotting factors is greatest within the first two to three days after the surgery, the dose required and levels are reduced thereafter. The checking of the levels and their frequency are highlighted. Further to the surgery, if physiotherapy is anticipated, directions are given as to when this should be safely undertaken – generally within the first few hours of the morning dose of concentrate, ensuring the level is at its peak.
- *Discharge advice*. Frequently, patients recover from their surgery sooner than the replacement factor therapy can be stopped. The patients are discharged at the discretion of the surgical team[22] and the haematology team is advised regarding the timing of surgical clips removal (if used) so that adequate factors level could be ensured. Further to discharge, on-going factor replacement programme is continued either through the CCC or via local hospitals, a link for which has been long established and works seamlessly. All patients are reviewed weekly within the CCC for three weeks after the operation, followed by routine review.

5. Conclusions

Our patients with inherited bleeding disorders undergoing non-orthopaedic surgery had low incidence of complications with no additional factors or treatment required over and above the amount stipulated in the protocol devised prior to surgery. No patient required blood transfusion. There was no mortality in this series. Surgery in patients with inherited bleeding disorders has become safer with the advent of multidisciplinary CCCs. Close communication between surgeon and haematologist is the key to successful management of these patients.

Ethical approval

This is a secondary research, ethical approval was not sought.

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Conflict of interest

None declared.

Author contribution

1. Jawad Ahmad: Study design, data collection, analysis, research and writing.
2. Gary M. Benson: Study design, data collection, analysis, research and writing.
3. Orla M. McNulty: Data collection.
4. Nathan Burnside: Literature review and writing.
5. Sadaf Gull: Literature review.
6. Imran K. Tailor: Data collection and writing.
7. Paul C. Winter: Review of paper.
8. Roy A.J. Spence: Study design, data collection, analysis, research and writing.

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